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(54) PROCEDE DE FABRICATION D'UNE FORME D'ADMINISTRATION SECURISEE CONTRE TOUT USAGE DETOURNE

(54) METHOD FOR THE PRODUCTION OF AN ADMINISTRATION FORM WHICH IS SECURED AGAINST MISUSE

(57)

The invention relates to a method for the production of thermoformed administration forms, which are secured against misuse, containing at least one synthetic or natural polymer with a breaking resistance of at least 500 N, in addition to one or several active substances having a misuse potential and, optionally, physiologically compatible auxiliary substances.

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(54) Titre : PROCEDE DE FABRICATION D'UNE FORME D'ADMINISTRATION SECURISEE CONTRE TOUT USAGE DETOURNE

(54) Title: METHOD FOR THE PRODUCTION OF AN ADMINISTRATION FORM WHICH IS SECURED AGAINST MISUSE

(57) Abrégé/Abstract:
The invention relates to a method for the production of thermoformed administration forms, which are secured against misuse, containing at least one synthetic or natural polymer with a breaking resistance of at least 500 N, in addition to one or several active substances having a misuse potential and, optionally, physiologically compatible auxiliary substances.

Abstract

The present invention relates to a process for the production of abuse-proofed, thermoformed dosage forms containing, apart from one or more active ingredients with potential for abuse and optionally physiologically acceptable auxiliary substances, at least one synthetic or natural polymer with a breaking strength of at least 500 N.

Process for the production of an abuse-proofed dosage form

The present invention relates to a process for the production of solid pharmaceutical dosage forms with at least reduced potential for abuse, by

a) shaping a formulation mixture containing at least one active ingredient with potential for abuse and at least one synthetic or natural polymer (C), which exhibits a breaking strength of at least 500 N, into formed articles by application of force,
b) optionally singulating the formed articles and optionally in each case grading them by size and,
c) after or during heating at least to the softening point of the polymer (C), exposing the formed articles to force until they have a breaking hardness of at least 500 N, optionally providing them with a cover and optionally mixing all the formed articles back together again.

Many pharmaceutical active ingredients, in addition to having excellent activity in their appropriate application, also have potential for abuse, i.e. they can be used by an abuser to bring about effects other than those intended.
Opiates, for example, which are highly active in combating severe to very severe pain, are frequently used by abusers to induce a state of narcosis or euphoria.

In order to make abuse possible, the corresponding dosage forms, such as tablets or capsules are comminuted, for example ground in a mortar, by the abuser, the active ingredient is extracted from the resultant powder using a preferably aqueous liquid and the resultant solution, optionally after being filtered through cotton wool or cellulose wadding, is administered parenterally, in particular intravenously. An additional phenomenon of this kind of administration, in comparison with abusive oral administration, is a further accelerated increase in active ingredient levels giving the abuser the desired effect, namely the "kick" or "rush". This kick is also obtained if the powdered dosage form is administered nasally, i.e. is sniffed.

Since delayed-release dosage forms containing active ingredients with potential for abuse do not give rise to the kick desired by the abuser when taken orally even in abusively high quantities, such dosage forms are also comminuted and extracted in order to be abused.

US-A-4,070,494 proposed adding a swellable agent to the dosage form in order to prevent abuse. When water is added to extract the active ingredient, this agent swells and ensures that the filtrate separated from the gel contains only a small quantity of active ingredient.

The multilayer tablet disclosed in WO 95/20947 is based on a similar approach to preventing parenteral abuse, said tablet containing the active ingredient with potential for abuse and at least one gel former, each in different layers.

WO 03/015531 A2 discloses another approach to preventing parenteral abuse. A dosage form containing an analgesic opioid and a dye as an aversive agent is described therein. The colour released by tampering with the dosage form is intended to discourage the abuser from using the dosage form which has been tampered with.

Another known option for complicating abuse involves adding antagonists to the active ingredients to the dosage form, for example naloxone or naltrexone in the case of opiates, or compounds which cause a physiological defence response, such as for example ipecacuanha (ipecac) root.

Since, however, as in the past, it is in most cases necessary for the purposes of abuse to pulverise dosage forms containing an active ingredient suitable for abuse, it was the object of the present invention to provide a process for the production of abuse-proofed dosage forms with which the pulverisation of the dosage form which precedes abuse using the means conventionally available to the potential abuser is complicated or prevented and thus to produce a dosage form for active ingredients with potential for abuse, which, when correctly administered, ensures the desired therapeutic action, but from which the active ingredient cannot be converted into a form suitable for abuse simply by pulverisation.

Said object has been achieved by the process according to the invention for the production of solid pharmaceutical dosage forms with at least reduced potential for abuse which is characterised in that

a) a formulation mixture containing at least one active ingredient with potential for abuse, at least one synthetic or natural polymer (C), which exhibits a breaking strength of at least 500 N, and optionally auxiliary substances (B) is shaped into formed articles by application of force,
b) the formed articles are optionally singulated and optionally in each case graded by size and,
c) after or during heating at least to the softening point of the polymer (C), the formed articles are exposed to force until they have a breaking hardness of at least 500 N, they are optionally provided with a cover and all the formed articles are optionally mixed back together again.

The use of polymers (C) having the stated minimum breaking strength in the process according to the invention, preferably in quantities such that the dosage form also exhibits such a minimum breaking strength, means that pulverisation of the dosage form is considerably more difficult using conventional means, so considerably complicating or preventing the subsequent abuse.

If comminution is inadequate, parenteral, in particular intravenous, administration cannot be performed safely or extraction of the active ingredient therefrom takes too long for the abuser or there is no "kick" when taken orally, as release is not instantaneous.

According to the invention, comminution is taken to mean pulverisation of the dosage form by the application of force with conventional means which are conventionally available to an abuser, such as for example a pestle and mortar, a hammer, a mallet or other usual means for pulverisation, wherein the proportion of fines which may arise (particle size equal to or smaller than 0.3 mm) must not exceed 5 wt.%.

The dosage form obtained according to the invention is thus suitable for preventing parenteral, nasal and/or oral abuse of pharmaceutical active ingredients with potential for abuse.

Pharmaceutical active ingredients with potential for abuse are known to the person skilled in the art, as are the quantities thereof to be used and processes for the production thereof, and may be present in the dosage form according to the invention as such, in the form of the corresponding derivatives thereof, in particular esters or ethers, or in each case in the form of corresponding physiologically acceptable compounds, in particular in the form of the salts or solvates thereof, as racemates or stereoisomers. The dosage form obtained according to the invention is also suitable for the administration of a plurality of active ingredients. It is preferably used for the administration of one specific active ingredient.

The dosage form obtained according to the invention is in particular suitable for preventing the abuse of at least one pharmaceutical active ingredient which is selected from the group comprising opiates, opioids, tranquillisers, preferably benzodiazepines, barbiturates, stimulants and further narcotics.

The dosage form obtained according to the invention is very particularly preferably suitable for preventing abuse of an opiate, opioid, tranquilliser or another narcotic, which is selected from the group comprising N-{{1-[2-(4-ethyl-5-oxo-2-tetrazolin-1-yl)ethyl]-4-methoxymethyl-4-piperidyl}propionanilide (alfentanil), 5,5-diallylbarbituric acid (allobarbital), allylprodine, alphaprodine, 8-chloro-1-methyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-a][1,4]-benzodiazepine (alprazolam), 2-diethylaminopropiophenone (amfepramone), (±)-α-methylphenethylamine (amphetamine), 2-(α-methylphenethylamino)-2-phenylacetonitrile (amphetaminil), 5-ethyl-5-isopentylbarbituric acid (amobarbital), anileridine, apocodeine, 5,5-diethylbarbituric acid (barbital), benzylmorphine, bezitramide, 7-bromo-5-(2-pyridyl)-1*H*-1,4-benzodiazepine-2(3*H*)-one (bromazepam), 2-bromo-4-(2-chlorophenyl)-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-a][1,4]diazepine (brotizolam), 17-cyclopropylmethyl-4,5 α-epoxy-7α[(S)-1-hydroxy-1,2,2-trimethyl-propyl]-6-methoxy-6,14-*endo*-ethanomorphinan-3-ol (buprenorphine), 5-butyl-5-ethylbarbituric acid (butobarbital), butorphanol, (7-chloro-1,3-dihydro-1-methyl-2-oxo-5-phenyl-2*H*-1,4-

benzodiazepin-3-yl) dimethylcarbamate (camazepam), (1*S*,2*S*)-2-amino-1-phenyl-1-propanol (cathine/D-norpseudoephedrine), 7-chloro-*N*-methyl-5-phenyl-3*H*-1,4-benzodiazepin-2-ylamine 4-oxide (chlordiazepoxide), 7-chloro-1-methyl-5-phenyl-1*H*-1,5-benzodiazepine-2,4(3*H*,5*H*)-dione (clobazam), 5-(2-chlorophenyl)-7-nitro-1*H*-1,4-benzodiazepin-2(3*H*)-one (clonazepam), clonitazene, 7-chloro-2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepine-3-carboxylic acid (clorazepate), 5-(2-chlorophenyl)-7-ethyl-1-methyl-1*H*-thieno[2,3-e][1,4]diazepin-2(3*H*)-one (clotiazepam), 10-chloro-11b-(2-chlorophenyl)-2,3,7,11b-tetrahydrooxazolo[3,2-*d*][1,4]benzodiazepin-6(5*H*)-one (cloxazolam), (-)-methyl-[3β-benzoyloxy-2β(1αH,5α*H*)-tropane carboxylate] (cocaine), 4,5α-epoxy-3-methoxy-17-methyl-7-morphinen-6α-ol (codeine), 5-(1-cyclohexenyl)-5-ethylbarbituric acid (cyclobarbital), cyclorphan, cyprenorphine, 7-chloro-5-(2-chlorophenyl)-1*H*-1,4-benzodiazepin-2(3*H*)-one (delorazepam), desomorphine, dextromoramide, (+)-(1-benzyl-3-dimethylamino-2-methyl-1-phenylpropyl)propionate (dextropropoxyphene), dezocine, diampromide, diamorphone, 7-chloro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (diazepam), 4,5α-epoxy-3-methoxy-17-methyl-6α-morphinanol (dihydrocodeine), 4,5α-epoxy-17-methyl-3,6a-morphinandiol (dihydromorphine), dimenoxadol, dimephetamol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, (6a*R*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6*H*-benzo[c]chromen-1-ol (dronabinol), eptazocine, 8-chloro-6-phenyl-4*H*-[1,2,4]triazolo[4,3-(a)][1,4]benzodiazepine (estazolam), ethoheptazine, ethylmethylthiambutene, ethyl [7-chloro-5-(2-fluorophenyl)-2,3-dihydro-2-oxo-1*H*-1,4-benzodiazepine-3-carboxylate] (ethyl loflazepate), 4,5α-epoxy-3-ethoxy-17-methyl-7-morphinen-6α-ol (ethylmorphine), etonitazene, 4,5α-epoxy-7α-(1-hydroxy-1-methylbutyl)-6-methoxy-17-methyl-6,14-*endo*-etheno-morphinan-3-ol (etorphine), *N*-ethyl-3-phenyl-8,9,10-trinorbornan-2-ylamine (fencamfamine), 7-[2-(α-methylphenethylamino)ethyl]-theophylline) (fenethylline), 3-(α-methylphenethylamino)propionitrile (fenproporex), *N*-(1-phenethyl-4-piperidyl)propionanilide (fentanyl), 7-chloro-5-(2-fluorophenyl)-1-methyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (fludiazepam), 5-(2-fluorophenyl)-1-methyl-7-nitro-1*H*-1,4-benzodiazepin-2(3*H*)-one (flunitrazepam), 7-chloro-1-(2-diethylaminoethyl)-5-(2-fluorophenyl)-1*H*-1,4-benzodiazepin-2(3*H*)-one (flurazepam), 7-chloro-5-phenyl-1-(2,2,2-trifluoroethyl)-1*H*-1,4-benzodiazepin-2(3*H*)-one (halazepam), 10-bromo-11b-(2-fluorophenyl)-2,3,7,11b-tetrahydro[1,3]oxazolo[3,2-d][1,4]benzodiazepin-6(5*H*)-one (haloxazolam), heroin, 4,5α-epoxy-3-methoxy-17-methyl-6-morphinanone

(hydrocodone), 4,5α-epoxy-3-hydroxy-17-methyl-6-morphinanone (hydromorphone), hydroxypethidine, isomethadone, hydroxymethylmorphinan, 11-chloro-8,12b-dihydro-2,8-dimethyl-12b-phenyl-4*H*-[1,3]oxazino[3,2-d][1,4]benzodiazepine-4,7(6*H*)-dione (ketazolam), 1-[4-(3-hydroxyphenyl)-1-methyl-4-piperidyl]-1-propanone (ketobemidone), (3*S*,6*S*)-6-dimethylamino-4,4-diphenylheptan-3-yl acetate (levacetylmethadol (LAAM)), (-)-6-dimethylamino-4,4-diphenol-3-heptanone (levomethadone), (-)-17-methyl-3-morphinanol (levorphanol), levophenacylmorphane, lofentanil, 6-(2-chlorophenyl)-2-(4-methyl-1-piperazinylmethylene)-8-nitro-2*H*-imidazo[1,2-a][1,4]-benzodiazepin-1(4*H*)-one (loprazolam), 7-chloro-5-(2-chlorophenyl)-3-hydroxy-1*H*-1,4-benzodiazepin-2(3*H*)-one (lorazepam), 7-chloro-5-(2-chlorophenyl)-3-hydroxy-1-methyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (lormetazepam), 5-(4-chlorophenyl)-2,5-dihydro-3*H*-imidazo[2,1-*a*]isoindol-5-ol (mazindol), 7-chloro-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine (medazepam), *N*-(3-chloropropyl)-α-methylphenethylamine (mefenorex), meperidine, 2-methyl-2-propyltrimethylene dicarbamate (meprobamate), meptazinol, metazocine, methylmorphine, N,α-dimethylphenethylamine (methamphetamine), (±)-6-dimethylamino-4,4-diphenol-3-heptanone (methadone), 2-methyl-3-*o*-tolyl-4(3*H*)-quinazolinone (methaqualone), methyl [2-phenyl-2-(2-piperidyl)acetate] (methylphenidate), 5-ethyl-1-methyl-5-phenylbarbituric acid (methylphenobarbital), 3,3-diethyl-5-methyl-2,4-piperidinedione (methyprylon), metopon, 8-chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5*a*][1,4]benzodiazepine (midazolam), 2-(benzhydrylsulfinyl)acetamide (modafinil), 4,5α-epoxy-17-methyl-7-morphinen-3,6α-diol (morphine), myrophine, (±)-*trans*-3-(1,1-dimethylheptyl)-7,8,10,10α-tetrahydro-1-hydroxy-6,6-dimethyl-6*H*-dibenzo-[*b, d*]pyran-9(6α*H*)-one (nabilone), nalbuphene, nalorphine, narceine, nicomorphine, 1-methyl-7-nitro-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (nimetazepam), 7-nitro-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (nitrazepam), 7-chloro-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (nordazepam), norlevorphanol, 6-dimethylamino-4,4-diphenyl-3-hexanone (normethadone), normorphine, norpipanone, the exudation from plants belonging to the species Papaver somniferum (opium), 7-chloro-3-hydroxy-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (oxazepam), (*cis-trans*)-10-chloro-2,3,7,11b-tetrahydro-2-methyl-11b-phenyloxazolo[3,2-*d*][1,4]benzodiazepin-6-(5*H*)-one (oxazolam), 4,5α-epoxy-14-hydroxy-3-methoxy-17-methyl-6-morphinanone (oxycodone), oxymorphone, plants

and parts of plants belonging to the species Papaver somniferum (including the subspecies setigerum) (Papaver somniferum), papaveretum, 2-imino-5-phenyl-4-oxazolidinone (pernoline), 1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol (pentazocine), 5-ethyl-5-(1-methylbutyl)-barbituric acid (pentobarbital), ethyl-(1-methyl-4-phenyl-4-piperidinecarboxylate) (pethidine), phenadoxone, phenomorphane, phenazocine, phenoperidine, piminodine, pholcodeine, 3-methyl-2-phenylmorpholine (phenmetrazine), 5-ethyl-5-phenylbarbituric acid (phenobarbital), α,α-dimethylphenethylamine (phentermine), 7-chloro-5-phenyl-1-(2-propynyl)-1*H*-1,4-benzodiazepin-2(3*H*)-one (pinazepam), α-(2-piperidyl)benzhydryl alcohol (pipradrol), 1'-(3-cyano-3,3-diphenylpropyl)[1,4'-bipiperidine]-4'-carboxamide (piritramide), 7-chloro-1-(cyclopropylmethyl)-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (prazepam), profadol, proheptazine, promedol, properidine, propoxyphene, N-(1-methyl-2-piperidinoethyl)-N-(2-pyridyl)propionamide, methyl {3-[4-methoxycarbonyl-4-(*N*-phenylpropanamido)piperidino]propanoate} (remifentanil), 5-*sec*-butyl-5-ethylbarbituric acid (secbutabarbital), 5-allyl-5-(1-methylbutyl)-barbituric acid (secobarbital), *N*-{4-methoxymethyl-1-[2-(2-thienyl)ethyl]-4-piperidyl}propionanilide (sufentanil), 7-chloro-2-hydroxy-methyl-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (temazepam), 7-chloro-5-(1-cyclohexenyl)-1-methyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (tetrazepam), ethyl (2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate) (tilidine (cis and trans)), tramadol, 8-chloro-6-(2-chlorophenyl)-1-methyl-4*H*-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine (triazolam), 5-(1-methylbutyl)-5-vinylbarbituric acid (vinylbital), (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol, (1R,2R,4S)-2-(dimethylamino)methyl-4-(p-fluorobenzyloxy)-1-(m-methoxyphenyl)cyclohexanol, (1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)phenol, (1S,2S)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol, (2R,3R)-1-dimethylamino-3(3-methoxyphenyl)-2-methyl-pentan-3-ol, (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-methoxyphenyl)-cyclohexane-1,3-diol, preferably as racemate, 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)phenyl 2-(4-isobutoxy-phenyl)-propionate, 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)phenyl 2-(6-methoxy-naphthalen-2-yl)-propionate, 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-(4-isobutyl-phenyl)-propionate, 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-(6-methoxy-naphthalen-2-yl)-propionate, (RR-SS)-2-acetoxy-4-trifluoromethyl-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl

ester, (RR-SS)-2-hydroxy-4-trifluoromethyl-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-4-chloro-2-hydroxy-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2-hydroxy-4-methyl-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2-hydroxy-4-methoxy-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2-hydroxy-5-nitro-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2',4'-difluoro-3-hydroxy-biphenyl-4-carboxylic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester together with corresponding stereoisomeric compounds, in each case the corresponding derivatives thereof, in particular amides, esters or ethers, and in each case the physiologically acceptable compounds thereof, in particular the salts and solvates thereof, particularly preferably hydrochlorides.

The dosage form according to the invention is particularly suitable for preventing abuse of an opioid active ingredient selected from among the group comprising oxycodone, hydromorphone, morphine, tramadol and the physiologically acceptable derivatives or compounds thereof, preferably the salts and solvates thereof, preferably the hydrochlorides thereof.

The dosage form according to the invention is furthermore in particular suitable for preventing abuse of an opioid active ingredient selected from among the group comprising (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol, (2R,3R)-1-dimethylamino-3-(3-methoxyphenyl)-2-methyl-pentan-3-ol, (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-methoxyphenyl)-cyclohexane-1,3-diol, (1R,2R)-3-(2-dimethylaminonethyl-cyclohexyl)phenol, the physiologically acceptable salts thereof, preferably hydrochlorides, physiologically acceptable enantiomers, stereoisomers, diastereomers and racemates and the physiologically acceptable derivatives thereof, preferably ethers, esters or amides.

These compounds and the process for the production thereof are described in EP-A-693475 and EP-A-780369 respectively. The corresponding descriptions are hereby introduced as a reference and are deemed to be part of the disclosure.

In order to achieve the necessary breaking strength, at least one synthetic or natural polymer (C) which exhibits a breaking strength, measured using the method disclosed in the present application, of at least 500 N is used in the process according to the invention.

Preferably, at least one polymer is selected for this purpose from among the group comprising polyalkylene oxides, preferably polymethylene oxides, polyethylene oxides, polypropylene oxides, polyethylenes, polypropylenes, polyvinyl chlorides, polycarbonates, polystyrenes, polyacrylates, the copolymers thereof, and mixtures of at least two of the stated polymer classes or polymers. The polymers are distinguished by a molecular weight of at least 0.5 million, determined by rheological measurements. Thermoplastic polyalkylene oxides, such as polyethylene oxides, with a molecular weight of at least 0.5 million, preferably of at least 1 million to 15 million, determined by rheological measurements, are very particularly preferred. These polymers have a viscosity at 25°C of 4500 to 17600 cP, measured on a 5 wt.% aqueous solution using a model RVF Brookfield viscosimeter (spindle no. 2 / rotational speed 2 rpm), of 400 to 4000 cP, measured on a 2 wt.% aqueous solution using the stated viscosimeter (spindle no. 1 or 3 / rotational speed
10 rpm) or of 1650 to 10000 cP, measured on a 1 wt.% aqueous solution using the stated viscosimeter (spindle no. 2 / rotational speed 2 rpm).

The polymers are preferably used in powder form. They may be soluble in water.

Polymers (C) are present in the formulation mixture or in the dosage forms produced according to the invention in an amount of at least 30 wt.%, preferably of at least 50 wt.% to 99.9 wt.%, relative to the total quantity.

In order to achieve the necessary breaking strength of the dosage form obtained according to the invention, it is furthermore possible additionally to use at least one natural or synthetic wax (D) with a breaking strength, measured using the method disclosed in the present application, of at least 500 N.

Waxes with a softening point of at least 60°C are preferably used. Carnauba wax and beeswax are particularly preferred. Carnauba wax is very particularly preferred.

Carnauba wax is a natural wax which is obtained from the leaves of the carnauba palm and has a softening point of at least 80°C. When the wax component (D) is additionally used, it is used together with at least one polymer (C) in quantities such that the dosage form exhibits a breaking strength of at least 500 N.

Auxiliary substances (B) which may be used are those known auxiliary substances which are conventional for the formulation of solid dosage forms. These are preferably plasticisers, such as polyethylene glycols, auxiliary substances which influence active ingredient release, preferably hydrophobic or hydrophilic, preferably hydrophilic polymers, very particularly preferably hydroxypropylmethylcellulose, and/or antioxidants. Suitable antioxidants are ascorbic acid, butylhydroxyanisole, butylhydroxytoluene, salts of ascorbic acid, monothioglycerol, phosphorous acid, vitamin C, vitamin E and the derivatives thereof, sodium bisulfite, particularly preferably butylhydroxytoluene (BHT) or butylhydroxyanisole (BHA) and α-tocopherol.

The antioxidant is preferably used in quantities of 0.01 to 10 wt.%, preferably of 0.03 to 5 wt.%, relative to the total weight of the dosage form.

The abuse-proofed, solid dosage form is produced by initially mixing the active ingredient, the component (C), optionally the wax component (D), optionally auxiliary substances (B) and optionally at least one of the optionally present further abuse-preventing components (a) – (f) listed below and the resultant formulation mixture is shaped by application of force into formed articles, preferably the dosage form.

The formulation mixture is prepared in a mixer known to the person skilled in the art. The mixer may, for example, be a roll mixer, shaking mixer, shear mixer or compulsory mixer.

The resultant formulation mixture is preferably directly shaped by application of force into formed articles, preferably the dosage form, preferably without exposure to heat. The formulation mixture may, for example, be formed into tablets by direct tabletting. In direct tabletting, pressing is performed with the assistance of a tabletting tool, i.e. bottom punch, top punch and die.

The formulation mixture may also first be granulated and then shaped.

Shaping is preferably performed with application of force, a force of greater than or equal to 0.5 kN, preferably of 1 to 100 kN, being applied. The force is preferably exerted with the assistance of a press, preferably a tablet press, with shaping rollers or shaping belts equipped with rollers. The formulation mixture may also be extruded with the assistance of an extruder to yield a strand which is singulated into formed articles having the desired size. If heating also proceeds during application of force, heating should remain below 60°C.

If the formulation mixture is processed to yield multiparticulate formed articles, such as granules, pellets, these should have a minimum size of 0.5 mm, preferably a size of 1 to 3.5 mm. Before further processing, these formed articles, if they are not of a largely uniform size, are preferably graded by size. This grading may proceed with the assistance of a screening method.

In the further process step c), the formed articles are again exposed to force, wherein either before or during application of force the formed articles are heated at least to the softening point of the polymer (C), preferably to greater than or equal to 60°C. A force of at least 0.1 kN, preferably of 1 kN up to 120 kN, particularly preferably up to 100 kN, very particularly preferably up to at most 90 kN, is applied. As is known to any person skilled in the art, the duration of the treatment with force is dependent on the strength of the applied force, on the heating before or during the application of force and optionally on the size of the formed articles and may be determined by simple tests such that, after the application of force, the formed articles exhibit a breaking hardness of at least 500 N, measured using the method stated below.

The necessary heating may preferably be monitored by a temperature measurement in the interior of a formed article with the assistance of a temperature sensor.

Force may be applied continuously or discontinuously with the assistance of the above-stated apparatus. The entire process according to the invention may proceed continuously and discontinuously.

Figure 1 shows an apparatus with which the formed articles 1, in the present case tablets, are exposed after heating to force between shaping belts with pressure rollers 2. The shaping belts, which run parallel one above and one below, are here provided with means for accommodating the tablets. A foil/film, preferably an aluminium foil or a functional foil/film (not shown in Figure 1), may also run with the shaping belts such that, during the application of force, the formed article 1, in the present case a tablet, may simultaneously be provided with a cover. Formed articles covered in this manner may be divided into a desired number of joined dosage forms, such as for example blister packs.

The formed articles may be heated in the most varied manner. Heating in ovens, i.e. with the assistance of a heated gas atmosphere, or with radiant heat is preferred. Heating may also be effected by electromagnetic waves, in particular by microwaves. Apart from ovens which are loaded in discontinuous batches, tunnel ovens, in which the formed articles are continuously conveyed through these ovens, are also suitable. In a further preferred process variant, heat is also introduced into the formed articles (1) via the conveyor belt.
Heating preferably proceeds under a protective gas atmosphere, particularly preferably under a nitrogen atmosphere.

As already explained, force may be applied with the assistance of a tablet press, the formed articles being supplied heated to the die. In particular, this may also be combined with jacketed tablet production, wherein the outer envelope material which is applied by pressure may consist of auxiliary substances or of an active ingredient/auxiliary substance mixture.

A procedure in which the application of force according to c) is effected by shaping rollers (see Figure 1) is particularly preferred. In this procedure, the heated formed articles (1) are supplied to two contrarotating pressure rollers (2) which comprise profile recesses to accommodate the individual tablets. The application of force onto the heated formed articles (1) between the rollers gives rise to the desired breaking strength of the dosage form.

This procedure is also suitable for continuous performance, wherein the formed articles are supplied to the rollers by a conveyor belt, by means of which, before the force is applied to the formed articles, said articles are previously directly exposed to heating in the tunnel oven, under a radiation source or through the belt.

In a further preferred embodiment, the formed articles (1) are conveyed in a carrier (3), which comprises a profile for the formed articles (1) and is particularly preferably configured as a continuous conveyor belt. This carrier (3) is brought into alignment with a second shaping belt (5), which likewise comprises a partial profile of the formed articles (1), and forced is exerted onto both sides of the carrier belts. This procedure is shown in **Figure 2**.

In the process according to the invention, it may be advantageous to apply release agents onto the shaped profiles, in which force is applied to the formed articles, and onto the formed articles so that the formed articles may readily be detached again from the carrier belts or the pressure rollers. Suitable release agents are pharmaceutically conventional release agents, such as for example talcum, magnesium stearate. Preferred release agents are those which do not change their state of aggregation at the temperature of the process.

It may furthermore be advantageous to provide mechanical release aids in the apparatus with which force is applied, which release aids actively eject the formed articles after the application of force. This may for example proceed by holes through which a gas is blown under pressure or by mechanical punches.

The method according to the invention may be accelerated and optimised by rapidly cooling the formed articles after the application of force according to c). This may proceed, for example by conveying the formed articles into or through a cooling chamber or by introducing them into a cooling medium, such as for example into a liquid gas.

The dosage forms obtained according to the invention are distinguished in that, due to their hardness, they cannot be pulverised, for example by grinding even if cooled

to low temperatures. This virtually rules out oral or parenteral, in particular intravenous or nasal abuse.

However, in order to prevent any possible abuse in the event of comminution and/or pulverisation of the dosage form obtained according to the invention which has nevertheless been achieved by application of extreme force, the dosage forms obtained according to the invention may, in a preferred embodiment, contain further agents which complicate or prevent abuse as auxiliary substances (B).

The abuse-proofed dosage form obtained according to the invention, which comprises, apart from one or more active ingredients with potential for abuse, at least one hardening polymer (C) optionally auxiliary substances (B) and optionally at least one wax (D), may accordingly also comprise at least one of the following components (a)-(e) as optional further auxiliary substances (B):

(a) at least one substance which irritates the nasal passages and/or pharynx,

(b) at least one viscosity-increasing agent, which, with the assistance of a necessary minimum quantity of an aqueous liquid, preferably as an aqueous extract obtained from the dosage form, forms a gel which preferably remains visually distinguishable when introduced into a further quantity of an aqueous liquid,

(c) at least one antagonist for each of the active ingredients with potential for abuse,

(d) at least one emetic,

(e) at least one dye as an aversive agent,

(f) at least one bitter substance.

Components (a) to (f) are additionally each individually suitable for abuse-proofing the dosage form according to the invention. Accordingly, component (a) is preferably

suitable for proofing the dosage form against nasal, oral and/or parenteral, preferably intravenous, abuse, component (b) is preferably suitable for proofing against parenteral, particularly preferably intravenous and/or nasal abuse, component (c) is preferably suitable for proofing against nasal and/or parenteral, particularly preferably intravenous, abuse, component (d) is preferably suitable for proofing against parenteral, particularly preferably intravenous, and/or oral and/or nasal abuse, component (e) is suitable as a visual deterrent against oral or parenteral abuse and component (f) is suitable for proofing against oral or nasal abuse. Combined use according to the invention of at least one of the above-stated components makes it possible still more effectively to complicate abuse of dosage forms obtained according to the invention.

In one embodiment, the dosage form according to the invention may also comprise two or more of components (a)-(f) in a combination, preferably (a), (b) and optionally (c) and/or (f) and/or (e) or (a), (b) and optionally (d) and/or (f) and/or (e).

In another embodiment, the dosage form obtained according to the invention may comprise all of components (a)-(f).

If the dosage form obtained according to the invention comprises an abuse-preventing component (a), substances which irritate the nasal passages and/or pharynx which may be considered according to the invention are any substances which, when administered accordingly via the nasal passages and/or pharynx, bring about a physical reaction which is either so unpleasant for the abuser that he/she does not wish to or cannot continue administration, for example burning, or physiologically counteracts taking of the corresponding active ingredient, for example due to increased nasal secretion or sneezing. These substances which conventionally irritate the nasal passages and/or pharynx may also bring about a very unpleasant sensation or even unbearable pain when administered parenterally, in particular intravenously, such that the abuser does not wish to or cannot continue taking the substance.

Particularly suitable substances which irritate the nasal passages and/or pharynx are those which cause burning, itching, an urge to sneeze, increased formation of

secretions or a combination of at least two of these stimuli. Appropriate substances and the quantities thereof which are conventionally to be used are known per se to the person skilled in the art or may be identified by simple preliminary testing.

The substance which irritates the nasal passages and/or pharynx of component (a) is preferably based on one or more constituents or one or more plant parts of at least one hot substance drug.

Corresponding hot substance drugs are known per se to the person skilled in the art and are described, for example, in "Pharmazeutische Biologie - Drogen und ihre Inhaltsstoffe" by Prof. Dr. Hildebert Wagner, 2nd., revised edition, Gustav Fischer Verlag, Stuttgart-New York, 1982, pages 82 et seq.. The corresponding description is hereby introduced as a reference and is deemed to be part of the disclosure.

A dosage unit is taken to mean a separate or separable administration unit, such as for example a tablet or a capsule.

One or more constituents of at least one hot substance drug, selected from the group consisting of Allii sativi bulbus (garlic), Asari rhizoma cum herba (Asarum root and leaves), Calami rhizoma (calamus root), Capsici fructus (capsicum), Capsici fructus acer (cayenne pepper), Curcumae longae rhizoma (turmeric root), Curcumae xanthorrhizae rhizoma (Javanese turmeric root), Galangae rhizoma (galangal root), Myristicae semen (nutmeg), Piperis nigri fructus (pepper), Sinapis albae semen/Erucae semen (white mustard seed), Sinapis nigri semen (black mustard seed), Zedoariae rhizoma (zedoary root) and Zingiberis rhizoma (ginger root), particularly preferably from the group consisting of Capsici fructus (capsicum), Capsici fructus acer (cayenne pepper) and Piperis nigri fructus (pepper) may preferably be added as component (a) to the dosage form obtained by the process according to the invention

The constituents of the hot substance drugs preferably comprise o-methoxy(methyl)phenol compounds, acid amide compounds, mustard oils or sulfide compounds or compounds derived therefrom.

Particularly preferably, at least one constituent of the hot substance drugs is selected from the group consisting of myristicin, elemicin, isoeugenol, β-asarone, safrole, gingerols, xanthorrhizol, capsaicinoids, preferably capsaicin, capsaicin derivatives, such as N-vanillyl-9E-octadecenamide, dihydrocapsaicin, nordihydrocapsaicin, homocapsaicin, norcapsaicin and nomorcapsaicin, piperine, preferably trans-piperine, glucosinolates, preferably based on non-volatile mustard oils, particularly preferably based on p-hydroxybenzyl mustard oil, methylmercapto mustard oil or methylsulfonyl mustard oil, and compounds derived from these constituents.

The dosage form obtained according to the invention may preferably contain the plant parts of the corresponding hot substance drugs in a quantity of 0.01 to 30 wt.%, particularly preferably of 0.1 to 0.5 wt.%, in each case relative to the total weight of the dosage unit.
If one or more constituents of corresponding hot substance drugs are used, the quantity thereof in a dosage unit according to the invention preferably amounts to 0.001 to 0.005 wt.%, relative to the total weight of the dosage unit.

Another option for preventing abuse of the dosage form obtained according to the invention consists in adding at least one viscosity-increasing agent as a further abuse-preventing component (b) to the dosage form, which, with the assistance of a necessary minimum quantity of an aqueous liquid, forms a gel with the extract obtained from the dosage form, which gel is virtually impossible to administer safely and preferably remains visually distinguishable when introduced into a further quantity of an aqueous liquid.

For the purposes of the present invention, visually distinguishable means that the active ingredient-containing gel formed with the assistance of a necessary minimum quantity of aqueous liquid, when introduced, preferably with the assistance of a hypodermic needle, into a further quantity of aqueous liquid at 37°C, remains substantially insoluble and cohesive and cannot straightforwardly be dispersed in such a manner that it can safely be administered parenterally, in particular intravenously. The material preferably remains visually distinguishable for at least one minute, preferably for at least 10 minutes.

The increased viscosity of the extract makes it more difficult or even impossible for it to be passed through a needle or injected. If the gel remains visually distinguishable, this means that the gel obtained on introduction into a further quantity of aqueous liquid, for example by injection into blood, initially remains in the form of a largely cohesive thread, which, while it may indeed be broken up mechanically into smaller fragments, cannot be dispersed or even dissolved in such a manner that it can safely be administered parenterally, in particular intravenously. In combination with at least one optionally present component (a) to (e), this additionally leads to unpleasant burning, vomiting, bad flavour and/or visual deterrence.

Intravenous administration of such a gel would most probably result in obstruction of blood vessels, associated with serious damage to the health of the abuser.

In order to verify whether a viscosity-increasing agent is suitable as component (b) for use in the dosage form obtained according to the invention, the active ingredient is mixed with the viscosity-increasing agent and suspended in 10 ml of water at a temperature of 25°C. If this results in the formation of a gel which fulfils the above-stated conditions, the corresponding viscosity-increasing agent is suitable for preventing or averting abuse of the dosage forms according to the invention.

If component (b) is added to the dosage form obtained according to the invention, one or more viscosity-increasing agents are used which are selected from the group consisting of microcrystalline cellulose with 11 wt.% carboxymethylcellulose sodium (Avicel® RC 591), carboxymethylcellulose sodium (Blanose®, CMC-Na C300P®, Frimulsion BLC-5®, Tylose C300 P®), polyacrylic acid (Carbopol® 980 NF, Carbopol® 981), locust bean flour (Cesagum® LA-200, Cesagum® LID/150, Cesagum® LN-1), pectins, preferably from citrus fruits or apples (Cesapectin® HM Medium Rapid Set), waxy maize starch (C*Gel 04201®), sodium alginate (Frimulsion ALG (E401)®), guar flour (Frimulsion BM®, Polygum 26/1-75®), iota-carrageenan (Frimulsion D021®), karaya gum, gellan gum (Kelcogel F®, Kelcogel LT100®), galactomannan (Meyprogat 150 ®), tara stone flour (Polygum 43/1 ®), propylene glycol alginate (Protanal-Ester SD-LB®), sodium hyaluronate, tragacanth, tara gum (Vidogum SP 200®), fermented polysaccharide welan gum (K1A96), xanthan gum (Xantural 180®). Xanthans are particularly preferred. The names stated in brackets are the trade names by which

the materials are known commercially. In general, a quantity of 0.1 to 20 wt.%, particularly preferably of 0.1 to 15 wt.%, relative to the total weight of the dosage form, of the stated viscosity-increasing agent(s) is sufficient to fulfil the above-stated conditions.

The component (b) viscosity-increasing agents, where provided, are preferably present in the dosage form according to the invention in quantities of greater than or equal to 5 mg per dosage unit, i.e. per administration unit.

In a particularly preferred embodiment of the present invention, the viscosity-increasing agents used as component (b) are those which, on extraction from the dosage form with the necessary minimum quantity of aqueous liquid, form a gel which encloses air bubbles. The resultant gels are distinguished by a turbid appearance, which provides the potential abuser with an additional optical warning and discourages him/her from administering the gel parenterally.

Component (C) may also optionally serve as an additional viscosity-increasing agent, which forms a gel with the assistance of a necessary minimum quantity of aqueous liquid.

It is also possible to formulate the viscosity-increasing agent and the other constituents in the dosage form obtained according to the invention in a mutually spatially separated arrangement.

In order to discourage and prevent abuse, the dosage form obtained according to the invention may furthermore comprise component (c), namely one or more antagonists for the active ingredient or active ingredients with potential for abuse, wherein the antagonists are preferably spatially separated from the remaining constituents of the dosage form obtained according to the invention and, when correctly used, do not exert any effect.

Suitable antagonists for preventing abuse of the active ingredients are known per se to the person skilled in the art and may be present in the dosage form obtained according to the invention as such or in the form of corresponding derivatives, in

particular esters or ethers, or in each case in the form of corresponding physiologically acceptable compounds, in particular in the form of the salts or solvates thereof.

If the active ingredient present in the dosage form is an opiate or an opioid, the antagonist used is preferably an antagonist selected from the group comprising naloxone, naltrexone, nalmefene, nalid, nalmexone, nalorphine or naluphine, in each case optionally in the form of a corresponding physiologically acceptable compound, in particular in the form of a base, a salt or solvate. The corresponding antagonists, where component (c) is provided, are preferably used in a quantity of greater than or equal to 1 mg, particularly preferably in a quantity of 3 to 100 mg, very particularly preferably in a quantity of 5 to 50 mg per dosage form, i.e. per administration unit.

If the dosage form obtained according to the invention comprises a stimulant as active ingredient, the antagonist is preferably a neuroleptic, preferably at least one compound selected from the group consisting of haloperidol, promethazine, fluphenazine, perphenazine, levomepromazine, thioridazine, perazine, chlorpromazine, chlorprothixine, zuclopentixol, flupentixol, prothipendyl, zotepine, benperidol, pipamperone, melperone and bromperidol.

The dosage form obtained according to the invention preferably comprises these antagonists in a conventional therapeutic dose known to the person skilled in the art, particularly preferably in a quantity of twice to three times the conventional dose per administration unit.

If the combination to discourage and prevent abuse of the dosage form obtained according to the invention comprises component (d), it may comprise at least one emetic, which is preferably present in a spatially separated arrangement from the other components of the dosage form according to the invention and, when correctly used, is intended not to exert its effect in the body.

Suitable emetics for preventing abuse of an active ingredient are known per se to the person skilled in the art and may be present in the dosage form obtained according to the invention as such or in the form of corresponding derivatives, in particular

esters or ethers, or in each case in the form of corresponding physiologically acceptable compounds, in particular in the form of the salts or solvates thereof.

An emetic based on one or more constituents of ipecacuanha (ipecac) root, preferably based on the constituent emetine may preferably be considered in the dosage form obtained according to the invention, as are, for example, described in "Pharmazeutische Biologie - Drogen und ihre Inhaltsstoffe" by Prof. Dr. Hildebert Wagner, 2nd, revised edition, Gustav Fischer Verlag, Stuttgart, New York, 1982. The corresponding literature description is hereby introduced as a reference and is deemed to be part of the disclosure.

The dosage form obtained according to the invention may preferably comprise the emetic emetine as component (d), preferably in a quantity of greater than or equal to 3 mg, particularly preferably of greater than or equal to 10 mg and very particularly preferably in a quantity of greater than or equal to 20 mg per dosage form, i.e. administration unit.

Apomorphine may likewise preferably be used as an emetic in the abuse-proofing according to the invention, preferably in a quantity of $\geq$ 3 mg, particularly preferably of $\geq$ 5 mg and very particularly preferably of $\geq$ 7 mg per administration unit.

If the dosage form obtained according to the invention contains component (e) as an additional abuse-preventing auxiliary substance, the use of such a dye brings about an intense coloration of a corresponding aqueous solution, in particular when the attempt is made to extract the active ingredient for parenteral, preferably intravenous administration, which coloration may act as a deterrent to the potential abuser. Oral abuse, which conventionally begins by means of aqueous extraction of the active ingredient, may also be prevented by this coloration. Suitable dyes and the quantities required for the necessary deterrence may be found in WO 03/015531, wherein the corresponding disclosure should be deemed to be part of the present disclosure and is hereby introduced as a reference.

If the dosage form obtained according to the invention contains component (f) as a further abuse-preventing auxiliary substance, this addition of at least one bitter

substance and the consequent impairment of the flavour of the dosage form additionally prevents oral and/or nasal abuse.

Suitable bitter substances and the quantities effective for use may be found in US-2003/0064099 A1, the corresponding disclosure of which should be deemed to be the disclosure of the present application and is hereby introduced as a reference. Suitable bitter substances are preferably aromatic oils, preferably peppermint oil, eucalyptus oil, bitter almond oil, menthol, fruit aroma substances, preferably aroma substances from lemons, oranges, limes, grapefruit or mixtures thereof, and/or denatonium benzoate. Denatonium benzoate is particularly preferred.

The solid dosage form obtained according to the invention is suitable for oral, vaginal or rectal administration, preferably for oral administration, to humans and animals. The dosage form is preferably not in film form. The orally administrable dosage form according to the invention may assume multiparticulate form, preferably in the form of microtablets, microcapsules, micropellets, granules, spheroids, beads or pellets, optionally packaged in capsules or pressed into tablets. The multiparticulate forms are preferably of a minimum size of 0.5 mm, particularly preferably in the range from 1 to 3.5 mm. Depending on the desired dosage form, conventional auxiliary substances (B) are optionally also used for the formulation of the dosage form.

In a further preferred embodiment, the dosage form according to the invention assumes the form of a tablet, a capsule or is in the form of an oral osmotic therapeutic system (OROS), preferably if at least one further abuse-preventing component (a)-(f) is also present.

If components (c) and/or (d) and/or (f) are present in the dosage form obtained according to the invention, care must be taken to ensure that they are formulated in such a manner or are present in such a low dose that, when correctly administered, the dosage form is able to bring about virtually no effect which impairs the patient or the efficacy of the active ingredient.

If the dosage form produced according to the invention contains component (d) and/or (f), the dosage must be selected such that, when correctly orally administered,

no negative effect is caused. If, however, the intended dosage of the dosage form is exceeded inadvertently, in particular by children, or in the event of abuse, nausea or an inclination to vomit or a bad flavour are produced. The particular quantity of component (d) and/or (f) which can still be tolerated by the patient in the event of correct oral administration may be determined by the person skilled in the art by simple preliminary testing.

If, however, irrespective of the fact that the dosage form produced according to the invention is virtually impossible to pulverise, the dosage form containing the components (c) and/or (d) and/or (f) is provided with protection, these components should preferably be used at a dosage which is sufficiently high that, when abusively administered, they bring about an intense negative effect on the abuser. This is preferably achieved by spatial separation of at least the active ingredient or active ingredients from components (c) and/or (d) and/or (f), wherein the active ingredient or active ingredients is/are present in at least one subunit (X) and components (c) and/or (d) and/or (f) is/are present in at least one subunit (Y), and wherein, when the dosage form is correctly administered, components (c), (d) and (f) do not exert their effect on taking and/or in the body and the remaining components of the formulation, in particular component (C), are identical.

If the dosage form according to the invention comprises at least 2 of components (c) and (d) or (f), these may each be present in the same or different subunits (Y). Preferably, when present, all the components (c) and (d) and (f) are present in one and the same subunit (Y).

For the purposes of the present invention, subunits are solid formulations, which in each case, apart from conventional auxiliary substances known to the person skilled in the art, contain the active ingredient(s), preferably also at least one polymer (C) and the optionally present component (D) and optionally at least one of the optionally present components (a) and/or (b) and/or (e) or preferably in each case at least one polymer (C) and optionally (D) and the antagonist(s) and/or emetic(s) and/or component (e) and/or component (f) and optionally at least one of the optionally present components (a) and/or (b). Care must here be taken to ensure that each of

the subunits is formulated in accordance with the above-stated process according to the invention, if the mechanical skill is desired or required.

One substantial advantage of the separated formulation of active ingredients from components (c) or (d) or (f) in subunits (X) and (Y) of the dosage form produced according to the invention is that, when correctly administered, components (c) and/or (d) and/or (f) are hardly released on taking and/or in the body or are released in such small quantities that they exert no effect which impairs the patient or therapeutic success or, on passing through the patient's body, they are only liberated in locations where they cannot be sufficiently absorbed to be effective. When the dosage form is correctly administered, preferably hardly any of components (c) and/or (d) and/or (f) is released into the patient's body or they go unnoticed by the patient.

The person skilled in the art will understand that the above-stated conditions may vary as a function of the particular components (c), (d) and/or (f) used and of the formulation of the subunits or the dosage form. The optimum formulation for the particular dosage form may be determined by simple preliminary testing. What is vital, if necessary for abuse prevention, is that each subunit contains the polymer (C) and has been formulated in the stated manner and produced according to the invention.

Should, contrary to expectations, the abuser succeed in comminuting such a dosage form according to the invention, which comprises components (c) and/or (e) and/or (d) and/or (f) in subunits (Y), for the purpose of abusing the active ingredient and obtain a powder which is extracted with a suitable extracting agent, not only the active ingredient but also the particular component (c) and/or (e) and/or (f) and/or (d) will be obtained in a form in which it cannot readily be separated from the active ingredient, such that when the dosage form which has been tampered with is administered, in particular by oral and/or parenteral administration, it will exert its effect on taking and/or in the body combined with an additional negative effect on the abuser corresponding to component (c) and/or (d) and/or (f) or, when the attempt is made to extract the active ingredient, the coloration will act as a deterrent and so prevent abuse of the dosage form.

A dosage form according to the invention, in which the active ingredient or active ingredients is/are spatially separated from components (c), (d) and/or (e), preferably by formulation in different subunits, may be formulated in many different ways, wherein the corresponding subunits may each be present in the dosage form according to the invention in any desired spatial arrangement relative to one another, provided that the above-stated conditions for the release of components (c) and/or (d) are fulfilled.

The person skilled in the art will understand that component(s) (a) and/or (b) which are optionally also present may preferably be formulated in the dosage form produced according to the invention both in the particular subunits (X) and (Y) and in the form of independent subunits corresponding to subunits (X) and (Y), provided that neither the abuse-proofing nor the active ingredient release in the event of correct administration is impaired by the nature of the formulation and the polymer (C) is preferably included in the formulation and formulation is preferably carried out in accordance with the process according to the invention.

In a preferred embodiment of the dosage form produced according to the invention, subunits (X) and (Y) are present in multiparticulate form, wherein granules, spheroids, beads or pellets are preferred and the same form, i.e. shape, is selected for both subunit (X) and subunit (Y), such that it is not possible to separate subunits (X) from (Y) by mechanical selection. The multiparticulate forms are preferably of a size in the range from 0.5 to 3.5 mm, preferably of 0.5 to 2 mm.

The subunits (X) and (Y) in multiparticulate form may also preferably be packaged in a capsule or be press-moulded into a tablet, wherein the final formulation in each case proceeds in such a manner that the subunits (X) and (Y) are also retained in the resultant dosage form.

The multiparticulate subunits (X) and (Y) of identical shape should also not be visually distinguishable from one another so that the abuser cannot separate them from one another by simple sorting. This may, for example, be achieved by the application of identical coatings which, apart from this disguising function, may also

incorporate further functions, such as, for example, delayed release of one or more active ingredients or provision of a finish resistant to gastric juices on the particular subunits.

The multiparticulate subunits may also be formulated as an oral dosage form as a slurry or suspension in pharmaceutically safe suspending media.

In a further preferred embodiment of the present invention, subunits (X) and (Y) are in each case arranged in layers relative to one another.

The layered subunits (X) and (Y) are preferably arranged for this purpose vertically or horizontally relative to one another in the dosage form produced according to the invention, wherein in each case one or more layered subunits (X) and one or more layered subunits (Y) may be present in the dosage form, such that, apart from the preferred layer sequences (X)-(Y) or (X)-(Y)-(X), any desired other layer sequences may be considered, optionally in combination with layers containing components (a) and/or (b).

Another preferred dosage form produced according to the invention is one in which subunit (Y) forms a core which is completely enclosed by subunit (X), wherein a separation layer (Z) may be present between said layers. Such a structure is preferably also suitable for the above-stated multiparticulate forms, wherein both subunits (X) and (Y) and an optionally present separation layer (Z), which should preferably satisfy the hardness requirement according to the invention, are then formulated in one and the same multiparticulate form using the process according to the invention.

In a further preferred embodiment of the dosage form produced according to the invention, the subunit (X) forms a core, which is enclosed by subunit (Y), wherein the latter comprises at least one channel which leads from the core to the surface of the dosage form.

The dosage form produced according to the invention may comprise, between one layer of the subunit (X) and one layer of the subunit (Y), in each case one or more,

preferably one, optionally swellable separation layer (Z) which serves to separate subunit (X) spatially from (Y).

If the dosage form produced according to the invention comprises the layered subunits (X) and (Y) and an optionally present separation layer (Z) in an at least partially vertical or horizontal arrangement, the dosage form preferably takes the form of a tablet, a coextrudate or a laminate, which has been produced using the process according to the invention.

In one particularly preferred embodiment, the entirety of the free surface of subunit (Y) and optionally at least part of the free surface of subunit(s) (X) and optionally at least part of the free surface of the optionally present separation layer(s) (Z) may be coated with at least one barrier layer (Z') which prevents release of component (c) and/or (e) and/or (d) and/or (f). The barrier layer (Z') should preferably also fulfil the hardness conditions according to the invention.

Another particularly preferred embodiment of the dosage form produced according to the invention comprises a vertical or horizontal arrangement of the layers of subunits (X) and (Y) and at least one push layer (p) arranged therebetween, and optionally a separation layer (Z), in which dosage form the entirety of the free surface of the layer structure consisting of subunits (X) and (Y), the push layer and the optionally present separation layer (Z) is provided with a semipermeable coating (E), which is permeable to a release medium, i.e. conventionally a physiological liquid, but substantially impermeable to the active ingredient and to component (c) and/or (d) and/or (f), and wherein this coating (E) comprises at least one opening for release of the active ingredient in the area of subunit (X).

A corresponding dosage form is known to the person skilled in the art, for example under the name oral osmotic therapeutic system (OROS), as are suitable materials and methods for the production thereof, inter alia from US 4,612,008, US 4,765,989 and US 4,783,337. The corresponding descriptions are hereby introduced as a reference and are deemed to be part of the disclosure.

In a further preferred embodiment, the subunit (X) of the dosage form produced according to the invention is in the form of a tablet, the edge face and optionally one of the two main faces of which is covered with a barrier layer (Z') containing component (c) and/or (d) and/or (f).

The person skilled in the art will understand that the auxiliary substances of the subunit(s) (X) or (Y) and of the optionally present separation layer(s) (Z) and/or of the barrier layer(s) (Z') used in the production according to the invention of the respective dosage form will vary as a function of the arrangement thereof in the dosage form, the mode of administration and as a function of the particular active ingredient of the optionally present components (a) and/or (b) and/or (e) and of component (c) and/or (d) and/or (f). The materials which have the requisite properties are in each case known per se to the person skilled in the art.

If release of component (c) and/or (d) and/or (f) from subunit (Y) of the dosage form produced according to the invention is prevented with the assistance of a cover, preferably a barrier layer, the subunit may consist of conventional materials known to the person skilled in the art, providing that they contain at least one polymer (C) and optionally (D) and have preferably been produced according to the invention.

If a corresponding barrier layer (Z') is not provided to prevent release of component (c) and/or (d) and/or (f), the materials of the subunits should be selected such that release of the particular component (c) and/or (d) from subunit (Y) is virtually ruled out.
The materials which are stated below to be suitable for production of the barrier layer may preferably be used for this purpose.

Preferred materials are those which are selected from the group comprising alkylcelluloses, hydroxyalkylcelluloses, glucans, scleroglucans, mannans, xanthans, copolymers of poly[bis(p-carboxyphenoxy)propane and sebacic acid, preferably in a molar ratio of 20:80 (commercially available under the name Polifeprosan 20®), carboxymethylcelluloses, cellulose ethers, cellulose esters, nitrocelluloses, polymers based on (meth)acrylic acid and the esters thereof, polyamides, polycarbonates, polyalkylenes, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates,

polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, halogenated polyvinyls, polyglycolides, polysiloxanes and polyurethanes and the copolymers thereof.

Particularly suitable materials may be selected from the group comprising methylcellulose, ethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxybutylmethylcellulose, cellulose acetate, cellulose propionate (of low, medium or high molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxymethylcellulose, cellulose triacetate, sodium cellulose sulfate, polymethyl methacrylate, polyethyl methacrylate, polybutyl methacrylate, polyisobutyl methacrylate, polyhexyl methacrylate, polyisodecyl methacrylate, polylauryl methacrylate, polyphenyl methacrylate, polymethyl acrylate, polyisopropyl acrylate, polyisobutyl acrylate, polyoctadecyl acrylate, polyethylene, low density polyethylene, high density polyethylene, polypropylene, polyethylene glycol, polyethylene oxide, polyethylene terephthalate, polyvinyl alcohol, polyvinyl isobutyl ether, polyvinyl acetate and polyvinyl chloride.

Particularly suitable copolymers may be selected from the group comprising copolymers of butyl methacrylate and isobutyl methacrylate, copolymers of methyl vinyl ether and maleic acid of high molecular weight, copolymers of methyl vinyl ether and maleic acid monoethyl ester, copolymers of methyl vinyl ether and maleic anhydride and copolymers of vinyl alcohol and vinyl acetate.

Further materials which are particularly suitable for formulating the barrier layer are starch-filled polycaprolactone (WO98/20073), aliphatic polyesteramides (DE 19 753 534 A1, DE 19 800 698 A1, EP 0 820 698 A1), aliphatic and aromatic polyester urethanes (DE 19822979), polyhydroxyalkanoates, in particular polyhydroxybutyrates, polyhydroxyvalerates, casein (DE 4 309 528), polylactides and copolylactides (EP 0 980 894 A1). The corresponding descriptions are hereby introduced as a reference and are deemed to be part of the disclosure.

The above-stated materials may optionally be blended with further conventional auxiliary substances known to the person skilled in the art, preferably selected from the group comprising glyceryl monostearate, semi-synthetic triglyceride derivatives,

semi-synthetic glycerides, hydrogenated castor oil, glyceryl palmitostearate, glyceryl behenate, polyvinylpyrrolidone, gelatine, magnesium stearate, stearic acid, sodium stearate, talcum, sodium benzoate, boric acid and colloidal silica, fatty acids, substituted triglycerides, glycerides, polyoxyalkylene glycols and the derivatives thereof.

If the dosage form produced according to the invention comprises a separation layer (Z'), said layer, like the uncovered subunit (Y), may preferably consist of the above-stated materials described for the barrier layer. The person skilled in the art will understand that release of the active ingredient or of component (c) and/or (d) from the particular subunit may be controlled by the thickness of the separation layer.

The dosage form produced according to the invention exhibits controlled release of the active ingredient. It is preferably suitable for repeated daily administration to patients, such as for example for combatting pain in human patients.

The dosage form produced according to the invention may comprise one or more active ingredients at least partially in a further delayed-release form, wherein delayed release may be achieved with the assistance of conventional materials and methods known to the person skilled in the art, for example by embedding the active ingredient in a delayed-release matrix or by the application of one or more delayed-release coatings. Active ingredient release must, however, be controlled such that the above-stated conditions are fulfilled in each case, for example that, in the event of correct administration of the dosage form, the active ingredient or active ingredients are virtually completely released before the optionally present component (c) and/or (d) can exert an impairing effect.

Addition of materials effecting controlled release must moreover not impair the necessary hardness.

Controlled release from the dosage form produced according to the invention is preferably achieved by embedding the active ingredient in a matrix. The auxiliary substances acting as matrix materials control active ingredient release. Matrix materials may, for example, be hydrophilic, gel-forming materials, from which active

ingredient release proceeds mainly by diffusion, or hydrophobic materials, from which active ingredient release proceeds mainly by diffusion from the pores in the matrix.

Physiologically acceptable, hydrophobic materials which are known to the person skilled in the art may be used as matrix materials. Polymers, particularly preferably cellulose ethers, cellulose esters and/or acrylic resins are preferably used as hydrophilic matrix materials. Ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxymethylcellulose, poly(meth)acrylic acid and/or the derivatives thereof, such as the salts, amides or esters thereof are very particularly preferably used as matrix materials.

Matrix materials prepared from hydrophobic materials, such as hydrophobic polymers, waxes, fats, long-chain fatty acids, fatty alcohols or corresponding esters or ethers or mixtures thereof are also preferred. Mono- or diglycerides of C12-C30 fatty acids and/or C12-C30 fatty alcohols and/or waxes or mixtures thereof are particularly preferably used as hydrophobic materials.

It is also possible to use mixtures of the above-stated hydrophilic and hydrophobic materials as matrix materials.

Component (C) and the optionally present component (D), which serve to achieve the breaking strength of at least 500 N which is obtained according to the invention, may furthermore themselves serve as additional matrix materials.

If the dosage form produced according to the invention is intended for oral administration, it may also preferably comprise a coating which is resistant to gastric juices and dissolves as a function of the pH value of the release environment.

By means of this coating, it is possible to ensure that the dosage form produced according to the invention passes through the stomach undissolved and the active ingredient is only released in the intestines. The coating which is resistant to gastric juices preferably dissolves at a pH value of between 5 and 7.5.

Corresponding materials and methods for the controlled release of active ingredients and for the application of coatings which are resistant to gastric juices are known to the person skilled in the art, for example from "Coated Pharmaceutical Dosage Forms - Fundamentals, Manufacturing Techniques, Biopharmaceutical Aspects, Test Methods and Raw Materials" by Kurt H. Bauer, K. Lehmann, Hermann P. Osterwald, Rothgang, Gerhart, 1st edition, 1998, Medpharm Scientific Publishers. The corresponding literature description is hereby introduced as a reference and is deemed to be part of the disclosure.

Method for determining breaking strength

A) In order to verify whether a polymer may be used as component (C) or (D), the polymer is pressed to form a tablet with a diameter of 10 mm and a height of 5 mm using a force of 150 N at a temperature which at least corresponds to the softening point of the polymer and is determined with the assistance of a DSC diagram of the polymer. Using tablets produced in this manner, breaking strength is determined with the apparatus described below in accordance with the method for determining the breaking strength of tablets published in the European Pharmacopoeia 1997, page 143, 144, method no. 2.9.8. The apparatus used for the measurement is a single column bench model materials tester with the designation "TMTC-FR2.5 TH.D09" from Zwick GmbH & Co. KG, Ulm, Germany, Fmax = 2.5 kN with a maximum draw of 1150 mm, which should be set up with one column and one spindle, a clearance behind of 100 mm and a test speed adjustable between 0.1 and 800 mm/min together with testControl software. Measurement is performed using a pressure piston with screw-in inserts and a cylinder (diam. 10 mm), a force transducer, Fmax. 1 kN, diameter = 8 mm, class 0.5 from 10 N, class 1 from 2 N to ISO 7500-1, with manufacturer's test certificate M to DIN 55350-18 (Zwick gross force Fmax = 1.45 kN) (all apparatus from Zwick GmbH & Co. KG, Ulm, Germany) with order no. BTC-FR 2.5 TH. D09 for the tester, order no. BTC-LC 0050N. P01 for the force transducer, order no. BO 70000 S06 for the centring device.

Figure 3 shows the measurement of the breaking strength of a tablet, in particular the tablet (4) adjustment device (6) used for this purpose before and during the measurement. To this end, the tablet (4) is held between the upper pressure plate (1) and the lower pressure plate (3) of the force application apparatus (not shown) with the assistance of two 2-part clamping devices, which are in each case firmly fastened (not shown) with the upper and lower pressure plate once the spacing (5) necessary for accommodating and centring the tablet to be measured has been established. The spacing (5) may be established by moving the 2-part clamping devices horizontally outwards or inwards in each case on the pressure plate on which they are mounted.

The tablets deemed to be resistant to breaking under a specific load include not only those which have not broken but also those which may have suffered plastic deformation under the action of the force.

The breaking strength of the dosage forms obtained according to the invention is determined by the stated measurement method, with dosage forms other than tablets also being tested.

The invention is explained below with reference to Examples. These explanations are given merely by way of example and do not restrict the general concept of the invention.

Examples:

Tramadol hydrochloride was used as the active ingredient in a series of Examples. Tramadol hydrochloride was used, despite tramadol not being an active ingredient which conventionally has potential for abuse, because it is not governed by German narcotics legislation, so simplifying the experimental work Tramadol is moreover a member of the opioid class with excellent water solubility.

Example 1:

Components	Per tablet	Complete batch
Tramadol HCl	100.0 mg	60.0 g
Polyethylene oxide, NF, MFI (190°C at 21.6 kg/10 min)MW 7,000,000 (Polyox WSR 303, Dow Chemicals)	221.0 mg	132.6 g
Hydroxypropylmethylcellulose 100,000 cP (Metholose 90 SH 100,000)	20.0 mg	12.0 g
Magnesium stearate	9.0 mg	5.4 g
Total weight	350.0 mg	210.0 g

Tramadol hydrochloride and polyethylene oxide powder and hydroxypropyl methylcellulose were mixed in a free-fall mixer. The magnesium stearate powder was then mixed in. The powder mixture was pressed into tablets on a Korsch EK0 eccentric press. The tabletting tool has a diameter of 10 mm and a radius of curvature of 8 mm. These tablets were further processed with the assistance of a laboratory heat sealer (Kopp laboratory sealer SPGE 20, Hot & Cold tack heat-sealed seam strength tester from Kopp). The heat sealing bars were replaced with two metal rails, into each of which had been milled a concavity having a diameter of 10 mm and a radius of 8 mm. The surface of the concavity is coated with Teflon. Once the bars have been fitted in the heat sealer, two complementary concavities produce a lens shape into which the tablets are in each case placed.
The heat sealing bars were heated in advance to 130°C, the tablets introduced and then a force of 750 N was exerted for 2.5 min.

The breaking strength of the tablets is determined using the above-described method. No breakage occurred when a force of 500 N was applied. The tablets could not be comminuted using a hammer, nor with the assistance of a pestle and mortar.

In vitro release of the active ingredient tramadol from the tablets was determined in a paddle stirrer apparatus with sinker in accordance with Pharm. Eur.. The temperature of the release medium was 37°C and the rotational speed of the stirrer 75 min^{-1}. The release medium used was an intestinal juice of pH 6.8. The quantity of active ingredient released in each case into the dissolution medium at any one time was determined by spectrophotometry.

Time	Quantity of active ingredient released
30 min	21%
240 min	70%
480 min	94%
720 min	100%

Example 2:

Components	Per tablet	Complete batch
Tramadol HCl	100.0 mg	60.0 g
Polyethylene oxide, NF, MFI (190°C at 21.6 kg/10 min)MW 5,000,000 (Polyox WSR Coagulant, Dow Chemicals)	221.0 mg	132.6 g
Hydroxypropylmethylcellulose 100,000 cP (Metholose 90 SH 100,000)	20.0 mg	12.0 g
Magnesium stearate	9.0 mg	5.4 g
Total weight	350.0 mg	210.0 g

As stated in Example 1, tablets with a diameter of 10 mm and a radius of curvature of 8 mm were produced.

The tablets were also further processed as in Example 1, except that the sealing bars were heated to 100°C.

The breaking strength of the tablets is determined using the above-described method. No breakage occurred when a force of 500 N was applied. The tablets could not be comminuted using a hammer, nor with the assistance of a pestle and mortar.

In vitro release of the active ingredient from the preparation was determined in a paddle stirrer apparatus with sinker in accordance with Pharm. Eur.. The temperature of the release medium was 37°C and the rotational speed of the stirrer 75 min^{-1}. The release medium used was an intestinal juice of pH 6,8. The quantity of active

ingredient released in each case into the dissolution medium at any one time was determined by spectrophotometry.

Time	Quantity of active ingredient released
30 min	17%
240 min	60%
480 min	84%
720 min	95%

Example 3:

Components	Per tablet	Complete batch
Tramadol HCl	100.0 mg	60.0 g
Polyethylene oxide, NF, MFI (190°C at 21.6 kg/10 min)MW 7,000,000, fine powder (Polyox WSR 303 FP, Dow Chemicals)	221.0 mg	132.6 g
Hydroxypropylmethylcellulose 100,000 cP (Metholose 90 SH 100,000)	20.0 mg	12.0 g
Magnesium stearate	9.0 mg	5.4 g
Total weight	350.0 mg	210.0 g

Tablets were produced as described in Example 1. The tablets were also further processed as explained in Example 1.

The breaking strength of the tablets was determined using the above-described method. No breakage occurred when a force of 500 N was applied. The tablets could not be comminuted using a hammer, nor with the assistance of a pestle and mortar.

In vitro release of the active ingredient from the preparation was determined in a paddle stirrer apparatus with sinker in accordance with Pharm. Eur.. The temperature of the release medium was 37°C and the rotational speed of the stirrer 75 min^{-1}. The release medium used was an intestinal juice of pH 6,8. The quantity of active ingredient released in each case into the dissolution medium at any one time was determined by spectrophotometry.

Time	Quantity of active ingredient released
30 min	21%
240 min	69%
480 min	93%
720 min	100%

Example 4:

Components	Per tablet	Complete batch
Tramadol HCl	100.0 mg	60.0 g
Polyethylene oxide, NF, MFI (190°C at 21.6 kg/10 min)MW 7,000,000 (Polyox WSR 303, Dow Chemicals)	221.0 mg	132.6 g
Hydroxypropylmethylcellulose 100,000 cP (Metholose 90 SH 100,000)	20.0 mg	12.0 g
Magnesium stearate	9.0 mg	5.4 g
Total weight	350.0 mg	210.0 g

Tablets were produced as stated in Example 1.

The tablets were then heated in a microwave oven for 10 min at 700 watts. Further processing proceeded as stated in Example 1, except that 2 bars each comprising 5 concavities were used and, using sealing bars heated to 100°C, in each case 5 heated tablets were exposed to a force of 1000 N for 30 seconds.

The breaking strength of the tablets is determined using the above-described method. No breakage occurred when a force of 500 N was applied. The tablets could not be comminuted using a hammer, nor with the assistance of a pestle and mortar.

Example 5:

Components	Per tablet	Complete batch
Tramadol HCl	100.0 mg	60.0 g
Polyethylene oxide, NF, MFI (190°C at 21.6 kg/10 min)MW 7,000,000 (Polyox WSR 303, Dow Chemicals)	221.0 mg	132.6 g
Hydroxypropylmethylcellulose 100,000 cP (Metholose 90 SH 100,000)	20.0 mg	12.0 g
Magnesium stearate	9.0 mg	5.4 g
Total weight	350.0 mg	210.0 g

Tablets were produced as stated in Example 1.

The tablets were then heated under an N_2 atmosphere in a circulating air cabinet for 45 min at 110°C. The tablets were further processed as stated in Example 4, except that the sealing bars were heated to 130°C.

The breaking strength of the tablets is determined using the above-described method. No breakage occurred when a force of 500 N was applied. The tablets could not be comminuted using a hammer, nor with the assistance of a pestle and mortar.

Example 6:

Components	Per tablet	Complete batch
Tramadol HCl	100.0 mg	60.0 g
Polyethylene oxide, NF, MFI (190°C at 21.6 kg/10 min)MW 7,000,000 (Polyox WSR 303, Dow Chemicals)	221.0 mg	132.6 g
Hydroxypropylmethylcellulose 100,000 cP (Metholose 90 SH 100,000)	20.0 mg	12.0 g
Magnesium stearate	9.0 mg	5.4 g
Total weight	350.0 mg	210.0 g

Tablets were produced as stated in Example 1.

Further processing proceeded as stated in Example 1, except that the sealing bars were heated to 130°C and the tablets were preheated in the lower bar for 2 minutes

while being exposed to a force of 10 N. The tablets were then post-compacted with a force of 1000 N at 130°C for 20 seconds.

The breaking strength of the tablets is determined using the above-described method. No breakage occurred when a force of 500 N was applied. The tablets could not be comminuted using a hammer, nor with the assistance of a pestle and mortar.

Example 7:

Components	Per tablet	Complete batch
Tramadol HCl	100 mg	18.2 g
Polyethylene oxide, NF, MW 7,000,000 (Polyox WSR 303 FP, Dow Chemicals)	165 mg	30.0 g
Polyethylene glycol 6000	7 mg	1.3 g
Butylhydroxytoluene	0.3 mg	0.1 g
Magnesium stearate	2.7 mg	0.5 g
Total weight	274.8 mg	50.0 g

The stated quantity of butylhydroxytoluene was dissolved in 0.6 g of ethanol (96%). This solution was mixed with the polyethylene glycol 6000 and then dried at 40°C for 12 hours. All the further components apart from magnesium stearate were added and mixed for 15 min in a free-fall mixer. The magnesium stearate was then mixed in. The mixture was screened with a 0.8 mm screen.

Using a Korsch EK0 eccentric press, tablets were produced from the screened mixture (diameter:10 mm and radius of curvature: 8 mm). These were then heated to 80°C in a drying cabinet under an N_2 atmosphere for 15 minutes.

The hot tablets were pressed again on an eccentric press (Kilian / IMA, model SP 300) with a force of 80 kN. The tool used was a tabletting punch with a diameter of 11 mm and a radius of curvature of 8 mm.

The breaking strength of the tablets was determined using the above-described method. No breakage occurred when a force of 500 N was applied. The tablets could not be comminuted using a hammer, nor with the assistance of a pestle and mortar.

In vitro release of the active ingredient from the preparation was determined in a paddle stirrer apparatus with sinker in accordance with Pharm. Eur.. The temperature of the release medium was 37°C and the rotational speed of the stirrer 75 min^{-1}. The release medium used was intestinal juice with a pH of 6.8. The quantity of active ingredient released in each case into the dissolution medium at any one time was determined by spectrophotometry.

Time	Quantity of active ingredient released
30 min	17%
240 min	65%
480 min	87%
720 min	95%

Claims:

1. A process for the production of a solid pharmaceutical dosage forms with at least reduced potential for abuse, characterised in that

    a) a formulation mixture containing at least one active ingredient with potential for abuse, at least one synthetic or natural polymer (C), which exhibits a breaking strength of at least 500 N, and optionally auxiliary substances (B) is shaped into formed articles by application of force,
    b) the formed articles are optionally singulated and optionally in each case graded by size and,
    c) after or during heating at least to the softening point of the polymer (C), the formed articles are exposed to force until they have a breaking hardness of at least 500 N, they are optionally provided with a cover and all the formed articles are optionally mixed back together again.

2. A process according to claim 1, characterised in that it is performed continuously or discontinuously.

3. A process according to claim 1 or claim 2, characterised in that the formulation mixture consists to an extent of at least 30 wt.% of component (C).

4. A process according to any one of claims 1 to 3, characterised in that the formulation mixture consists to an extent of at least 50 wt.% of component (C).

5. A method according to any one of claims 1 to 4, characterised in that a) shaping of the formulation mixture proceeds with application of a force of at least 0.5 kN and optionally with heating to less than 60°C.

6. A process according to any one of claims 1 to 5, characterised in that, according to c), the formed articles are heated to at least 60°C before or during application of force of at least 0.1 kN, preferably of 1 kN to 120 kN.

7. A process according to any one of claims 1 to 6, characterised in that the application of force according to a) or c) is performed with the assistance of a press, preferably a tablet press, shaping rollers or with shaping belts equipped with rollers.

8. A process according to any one of claims 1 to 7, characterised in that shaping according to a) gives rise to tablets.

9. A process according to any one of claims 1 to 7, characterised in that shaping according to a) gives rise to a multiparticulate dosage form with a minimum size of 0.5 mm, preferably of 1 to 3.5 mm.

10. A process according to any one of claims 1 to 9, characterised in that opioid active ingredients are used as active ingredients.

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Figures: 1+2+3

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Unscannable items
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Documents reçus avec cette demande ne pouvant être balayés
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